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REVIEW

Dendritic cells and parasites: from recognition and activation to immune response instruction

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Abstract The effective defense against parasite infections requires the ability to mount an appropriate and controlled specific immune response able to eradicate the invading pathogen while limiting the collateral damage to self-tissues. Dendritic cells are key elements for the development of immunity against parasites; they control the responses required to eliminate these pathogens while maintaining host homeostasis. Ligation of dendritic cell pattern recognition receptors by pathogen-associated molecular pattern present in the parasites initiates signaling pathways that lead to the production of surface and secreted proteins that are required, together with the antigen, to induce an appropriate and timely regulated immune response. There is evidence showing that parasites can influence and regulate dendritic cell functions in order to promote a more permissive environment for their survival. In this review, we will focus on new insights about the ability of protozoan and helminth parasites or their products to modify dendritic cell function and discuss how this interaction is crucial in shaping the host response.

Keywords Protozoa · Helminth · Th cell polarization · Tolerance · Tissue damage

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Introduction

The effective defense against infections requires the ability to mount an appropriate and controlled specific immune response able to eradicate the invading pathogen while limiting the collateral damage to self-tissues. The development of an effective immune response depends primarily on the type of pathogen; therefore, the pathogen is the main factor skewing the adaptive immune response in a particular direction [1]. The key players that transmit this information are professional antigen-presenting cells (APCs) such as dendritic cells (DCs) that, through the pattern recognition receptors (PRRs), sense the pathogen-associated molecular pattern (PAMPs) present in the microbes and produce surface and secreted proteins that are required, together with the antigen (Ag), to induce an appropriate and timely regulated adaptive immune response [2].

The DC-derived factors that determine the outcome of DC-T cell interactions are the histocompatibility complex II (MHC-II)-Ag presentation levels, the costimulatory molecules displayed, and the presence of immunomodulatory factors such as cytokines. While increased Ag presentation levels and the expression of costimulatory molecules, such as CD80, CD86, and CD40, on DCs are crucial for the expansion of Ag-specific T cells, the expression of coinhibitory molecules, such as programmed cell death-1 (PD-1) ligands, PD-L1 and PD-L2, can act synergistically to inhibit T cell activation, proliferation, and cytokine production [3]. In addition, stimuli that induce IL-12 promote IFN-γ-producing Th1 cells, stimuli that induce IL-10 and TGF-β favor regulatory T (Treg) cell differentiation, and stimuli that induce TGF-β and IL-6 promote a Th17 response in the mouse [4, 5]. In addition, IL-4 and IL-10 are both candidates for a Th2-driving signal from DC; however, it has been demonstrated that both IL-4- and IL-10-deficient DC can still drive Th2 responses [6].

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Host resistance to protozoa infections is dependent on the development of a Th1 response and the production of IL-12 by APCs [7]. Thus, the classical reaction of the host to protozoan parasite infections is the maturation of different DC subsets, and in some instances, the activity of these cells leads to a response that is effective in controlling the infection.

On the other hand, helminth infections induce a non-classical DC maturation and Th2 response that does not contribute with parasite elimination. Besides, it has been shown that both, helminths and protozoan, are capable to interfere with DC maturation and function, promoting a permissive environment for their own survival inside the host [8]. Here, we will focus on the ability of protozoan or helminth parasites or their products to modify DC function and the consequences of such modulation on the development of protective or pathogenic immune response and therefore on the outcome of the infection.

Parasite recognition by DC

Different receptors present in DCs are involved in the recognition of parasites. Toll-like (TLR) and C-type lectin (CLR) receptors are the most studied from all of the ones involved in the interaction with parasite-derived molecules, which is a crucial event in the mechanisms that lead to the altered function in these cells.

Recognition of parasite PAMPs by TLR

Protozoan parasites belong to the protista kingdom and are unicellular microorganisms that form a complete unit. They can carry out physiological functions by organelles and adapt to a special existence within the host. Infections with protozoan parasites are a world health problem. According to WHO reports, they cause around 720,000 deaths annually worldwide. Among protozoan parasites, those living in the human blood and tissues can cause fatal diseases such as malaria, visceral leishmaniasis, toxoplasmic encephalitis, and trypanosomiasis [9]. In their interactions with the host, the DCs may both sense the antigens released by the protozoa and internalize the full parasite. As an example, dermal DCs are capable of taking up the obligate intracellular parasite *Leishmania major* [10].

It has been almost two decades since TLRs were characterized, and since then, there has been a huge growth in the knowledge of viral, bacterial, and fungal ligands of TLR. Simultaneously, an important number of TLR ligands derived from protozoan parasites have also been identified. Thus, glycoinositolphospholipids (GIPLs) from *Trypanosoma cruzi* are recognized by TLR4 [11], while the glycosylphosphatidylinositol (GPI) anchors of *Trypanosoma cruzi* trypomastigotes and of intraerythrocytic *Plasmodium falciparum* are recognized by TLR2 inducing inflammatory cytokine response in macrophages and DCs [12–14]. DNA from *Trypanosoma cruzi* stimulates cytokine production by APCs in a TLR9-dependent manner and synergizes with the TLR2-ligand GPI anchor in the induction of cytokines by macrophages [15]. In addition, a protein-DNA complex from *Plasmodium falciparum* activates DC through TLR9 to produce inflammatory cytokines; the complex formation with proteins essential for the entry of parasite DNA into DC for TLR9 recognition [16].

The involvement of TLR in the anti-Leishmania immunity is evidenced by the fact that MyD88-deficient mice are more susceptible than are wild-type (wt) mice to the infection with *Leishmania major*. LPG, the most abundant surface molecule of *Leishmania* sp., signals through TLR2 to control the parasite growth and instructs the Th1 protective response [17]. In the same way, the P8 proteoglycolipid complex (P8 PGLC), expressed by the *Leishmania mexicana* parasite and *Leishmania pifanoi* amastigote, induces TLR4-dependent inflammatory cytokine secretion [18]. In addition, the induction of IL-12 and IFN-α/β in myeloid and plasmacytoid DC by intact *Leishmania major*, *L. infantum*, or their DNA has been demonstrated to be totally dependent on TLR9 signaling [19, 20]. Interestingly, although it has been reported that *Leishmania major*-infected TLR4-deficient mice or mice treated with a combination of anti-TLR2 and anti-TLR4 antibodies show impaired control of parasite growth and lack of protective Th1 response along with reduced costimulatory molecule expression on DC [21, 22], TLR2-deficient mice infected with *Leishmania braziliensis* show enhanced DC activation and increased IL-12 production, with TLR2 −/− DC being more competent to prime naive CD4+ T cells in vitro [23]. These findings suggest that TLR2 and TLR4 signals play a controversial role in the growth of *Leishmania* parasites in mice and that the ultimate effect of TLR2 and TLR4 on *Leishmania* infection in a given context (*Leishmania* species, host susceptibility, among others) is unknown.

Toxoplasma gondii is a promiscuous parasite that can infect any nucleated host cell, but it has a preference for cells of the immune system, among them the DCs [24]. IL-12 production by DC is often used as a measure of *Toxoplasma* recognition by these cells. It had been found that the IL-12 response of splenic DCs to soluble parasite extract (STAg) exceeded that of LPS and CpG oligonucleotides [25]. One of the first evidences of the involvement of TLR signaling in IL-12 production in response to *Toxoplasma* was the fact that splenic DCs from MyD88-deficient mice show defective IL-12 response to STAg [26]. In the search of TLR involved in DC activation, TLR11 was identified to signal after binding a *Toxoplasma* profilin (TgPRF) [27]. Later on, it was discovered that the 12 membrane-spanning endoplasmic reticulum-resident protein (UNC93B1) also interacts with TLR11 and regulates the activation of DCs [28]. The participation of other TLRs in the

recognition of *Toxoplasma gondii* and the subsequent change in the maturation of DC is not so clear yet. Some reports show that the absence of either TLR2 or TLR4 in DC does not modify the production of IL-12 in response to STAg [26], while other authors have reported the involvement of the TLR4-dependent MyD88-independent signaling pathway in *Toxoplasma gondii* HSP70-stimulated DC maturation [29]. Interestingly, mice deficient for TLR2, TLR4, or TLR11 survive *Toxoplasma gondii* infection [26, 27, 30], suggesting that the recognition of *Toxoplasma gondii* by the innate immune system depends on an additional MyD88-TLR-dependent signaling. In this respect, the binding of TgPRF to TLR12 has recently been reported [31]. This TLR is sufficient for the recognition of TgPRF by plasmacytoid DC, whereas TLR11 and TLR12 are required both in macrophages and in conventional DCs. In contrast to TLR11-deficient mice, TLR12-deficient mice succumb rapidly to *Toxoplasma gondii* infection [31].

Helminth or worms are multicellular organisms comprising a large number of parasites belonging to the animal kingdom, which infect a quarter of the world's population. Unlike protozoan parasites, helminths are macropathogens, a condition that prevents them from being ingested by phagocytic cells. However, they elicit a strong adaptive immune response through their derived secretions, namely, the excretory/secretory fraction (ES), which contain a complex mixture of proteins, lipids, and metabolic products that are released throughout their lifecycles and are recognized by PRR on APCs. A predominant Th2 response during helminth infections has been widely demonstrated, although the precise mechanism to initiate this response is not fully elucidated [8]. Despite this, it is clear that DCs are involved in the recognition of helminth or their products and the subsequent promotion of Th2 development.

The involvement of TLRs in the recognition of helminth or their products by CD has been widely reported [32]. TLR4 has been implicated in the recognition of ES-62 antigen from the filarial nematode *Acantamoeba viteae* by DC. However, unlike protozoan antigens, the signaling through TLR4 induces low levels of IL-12 and TNF and the development of Th2 response [33]. Besides, lacto-N-fucopentaose III (LNFPIII), a Lewis^X (LEX)-containing glycan found in *Schistosoma* soluble egg antigens (SEAs), is able to modulate DC activation to induce Th2 response through TLR4 signaling [34]. However, in vitro activation of DCs by SEA has been shown to be TLR4, TLR2, and MyD88 independent [35].

DC TLR2 is also involved in the recognition of helminth parasites, and their signaling has been linked to Th2 immunity. Phosphatidylserine (PS) lipids derived from *Schistosoma mansoni* eggs and adult worms or *Ascaris lumbricoides* worms were identified as TLR2 ligands. However, these molecules promote DC activation to drive Th2 responses in a TLR2-independent fashion [36], whereas monoacetylated PS from schistosomes induces TLR2-dependent DC maturation that promotes IL-10-secreting Treg cells [37]. Moreover, it has been recently reported that TLR2 signaling can direct PD-L2 expression on DC, which, through the PD-1-PD-L2 interaction, inhibits T cell response during *Schistosoma japonicum* infection [38]. Interestingly, the TLR3 sensing of double-stranded RNA from the egg stage of *Schistosoma mansoni* activates DCs to drive a Th1 response, but this signaling is dispensable to control infection or pathology [39].

Taken together, these data show that although some helminth-derived molecules are recognized by DC TLR2 and TLR4 and that signaling results in the promotion of a regulatory response, other non-TLRs are necessary for the initiation of Th2 responses.

Non-TLR DC receptors involved in the recognition of parasites

As we have described above, live *Toxoplasma gondii* tachyzoites or STAg have an unusual power to induce IL-12 production by DC through the activation of TLR signaling. Attempts to purify the *Toxoplasma gondii* molecules responsible for IL-12 induction led to the identification of an 18-kDa protein, an isoform of *Toxoplasma gondii* cyclophilin (C-18) that possesses an IL-12-inducing activity through the CCR5 chemokine receptor, presumably by a $G_{\alpha i}$ protein-dependent signaling pathway [40]. Interestingly, Aliberti et al. suggest that CCR5 binding by C-18 represents an example of molecular mimicry employed by *Toxoplasma gondii* [40].

It has been described that, after the interaction with TLRs, protozoan parasites stimulate DCs and promote the development of the appropriate protective immunity. Nevertheless, the binding or recognition of these parasites by non-TLR receptors such as CLRs or scavenger receptors leads to an inhibition of DC activation. In this way, the interaction of *Plasmodium falciparum* erythrocyte membrane protein 1 (PfEMP1) and the DC scavenger receptor CD36 inhibits DC maturation, inducing both the delayed antimalarial immunity as well as the immunosuppression associated with acute malaria infection [41]. Siglec-E, a sialic acid-binding Ig-like lectin, is an inhibitory receptor predominantly expressed on APCs as macrophages and DCs. The interaction between DC Siglec-E and sialylated ligands present in pathogenic, but not in non-pathogenic, *Trypanosoma cruzi* parasites leads to a diminished production of IL-12, which is critical for a protective Th1 response [42].

Interestingly, some interactions between DC CLR and parasites allow not only to modulate DC maturation [43] but also to participate in the phagocytosis of the pathogen. This is the case of dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN), a CLR expressed on DC that recognizes *Leishmania* parasites favoring their internalization [44]. Moreover, glycans from *Toxocara canis* or *Brugia*

malayi are involved in DC-SIGN recognition by DC as well as the induction of Th2 [45, 46]. SEA from *Schistosoma mansoni* is a complex mixture of diverse glycoproteins and glycolipids that can be sensed and internalized by DC through multiple CLRs such as mannose receptor (MR), macrophage galactose-type lectin (MGL), and DC-SIGN, with the SEA internalization being important to regulate DC response to TLR-induced signals [47]. Interestingly, a LEX-containing glycan found in SEA is critically involved in DC DC-SIGN recognition [48] and their Th2-driving capacity [49]. Besides, omega-1, a glycosylated T2 ribonuclease (RNase) secreted by *Schistosoma mansoni* eggs and present in SEA, is capable of conditioning human monocyte-derived DC in vitro to drive Th2 polarization [50]. Also, it has been recently reported that both glycosylation and RNase activity are critical to condition DC for Th2 polarization because omega-1 is internalized via its glycans by the MR, and subsequently, it impairs protein synthesis by degrading both ribosomal and messenger RNA [51].

The neglected tropical disease fasciolosis is a helminthiasis due to the trematodes *Fasciola hepatica* and *Fasciola gigantica* that infects around 17 million humans worldwide. A role for DC MR in the sensing of *Fasciola hepatica* tegumental antigens (FhTeg), which instructs DCs to drive CD4+ T cell anergy, has been recently reported [52]. In a similar way, glycans from *Fasciola hepatica* total extract (TE) inhibit DC maturation inducing Th2 response through MR signaling [53].

Taken together, these data show the ability of some helminth-derived glycans to modulate DC activation through CLR, to lead Th2-dominant responses.

Signaling pathways involved in the modulation of DC by parasites

The parasites have evolved strategies to interfere with a broad range of signaling processes in DC. This section focuses on how protozoan and helminth parasites modulate these signaling pathways to favor their survival and persistence in the host.

Inhibition of TLR-induced DC maturation

The interference in the TLR-induced DC maturation by protozoan parasites has been widely reported. *Plasmodium sp.*, *Leishmania sp.*, *Trypanosoma cruzi*, *Toxoplasma gondii*, and *Giardia lamblia* or their products have demonstrated their ability to inhibit TLR-induced DC maturation decreasing the production of inflammatory cytokines and/or the expression of MHC-II and costimulatory molecules or inducing the expression of coinhibitor molecules as PD-L2 [54–59]. For instance, DC from *Plasmodium yoelii*-infected mice become refractory to TLR-induced IL-12 and TNF production while showing increased ability to produce IL-10 [54]. In addition, Wykes et al. [55] have associated this block in DC function, which leads to an impaired Th1 immune response, with a lethal strain of *Plasmodium yoelii*. In the same line, *Trypanosoma cruzi* trypomastigotes prevent the full LPS-induced DC maturation, thereby downregulating MHC-II surface expression and inhibiting their capacity to stimulate lymphocyte proliferation, with both IL-10 and TGF-β involved in this last effect [56]. Recently, these authors have demonstrated that *Trypanosoma cruzi*-infected DCs upregulate Galectin-1, a glycan-binding protein involved in Th1 inhibition and Th2 response promotion [60], and they propose that Galectin-1 functions as a negative regulator to limit host-protective immunity [61].

The ability of live helminth parasites as microfilaria from *Brugia malayi* [62], as well as helminth-derived products from trematodes and cestodes to interfere with TLR-induced DC maturation has been extensively reported [32]. For instance, SEA from *Schistosoma mansoni* suppresses the LPS-induced activation of murine DC, including MHC-II, costimulatory molecule expression, and IL-12 production, partially through an IL-10-dependent mechanism [63]. Furthermore, purified helminth-derived antigens like the hydatid cyst component antigen B (AgB) from *Echinococcus granulosus* are able to downregulate CD1a expression and upregulate CD86 expression during human DC differentiation from monocyte precursors. In addition, DCs previously exposed to this antigen fail to upregulate CD80 and CD86 expression and to secrete TNF and IL-12p70 after LPS stimulation [64].

In a similar way, we have reported that ES products from *Fasciola hepatica* impair the ability of DC to be activated by TLR ligands, as well as their capacity to stimulate an allospecific response [65]. Interestingly, we took advantage of the ability of *Fasciola hepatica* TE to induce tolerogenic properties in CpG-maturated DC and evaluate the therapeutic potential of these cells to diminish the inflammatory response in collagen-induced arthritis (CIA). The vaccination of mice with bovine collagen II-pulsed TE/CpG-conditioned DC diminishes the severity and incidence of CIA symptoms and the production of inflammatory cytokines, while it induces the production of anti-inflammatory cytokines and Treg [66]. In addition, we identified a Kunitz-type molecule (Fh-KTM), present in a low molecular weight fraction from *Fasciola hepatica* TE, as responsible for suppressing the proinflammatory cytokine production in LPS-activated DCs [67]. Taken together, these findings suggest that parasites may modulate DCs to favor a suppressive environment, which may help parasite establishment, minimizing the excessive inflammation which may lead to tissue damage.

Regulation of MAPK- and PI3K-mediated pathways

Mitogen-activated protein kinases (MAPKs) are a group of serine/threonine-specific protein kinases that constitute one of the most important intracellular signaling pathways in DCs that regulate their accessory and effector functions including the production of cytokines [68, 69]. Therefore, DC maturation status depends on the balance of this particular molecular signaling cascade. The MAPK family is composed of the extracellular signal-related kinases 1 and 2 (ERK 1/2), c-jun NH2-terminal kinase (JNK), and p38 MAPK. The activation of these kinases, by upstream kinases, activates a number of selected intracellular proteins and transcription factors such as activating protein 1 (AP-1), NF-κB, and IFN regulatory factors (IRFs) through which a diverse signaling cascade that regulates gene expression is triggered [70].

JNK and p38 activation has been associated to DC activation, maturation, proinflammatory cytokine secretion, and Th1 induction [69]. As described above, infection with protozoan parasites or the interaction with protozoa antigens mostly induce phenotypic maturation of DCs and secretion of proinflammatory cytokines. Accordingly, *Giardia lamblia* binding immunoglobulin protein (GlBiP) from *Giardia lamblia* and Gal-lectin from the protozoan intestinal parasite *Entamoeba histolytica* induce upregulation of CD80, CD86, and MHC-II expressions and proinflammatory cytokine secretion from mouse DCs through the activation of MAPKs and increased activity of NF-κB [71, 72]. In the same way, during *Trypanosoma cruzi* infection, MIF-induced early DC maturation and IL-12 production mediates resistance to *Trypanosoma cruzi* infection by activation of the p38 pathway [73]. In line with these findings, the absence of MAPK phosphatase 5 (MKP5), a negative regulator of JNK and p38 MAPK activities, increases host resistance to the lethal *Plasmodium yoelii* 17XL infection by the enhancement of the protective IFN-γ response [68]. In addition, splenic CDs from infected MKP5 deficient mice show an enhanced ability to induce IFN-γ production by $CD4^+$ T cells [68]. In addition, human monocyte-derived DCs cultured with *Plasmodium falciparum* iRBCs show a p38-MAPK-dependent semimature phenotype that responds to CD40 signaling by maturing and secreting increased levels of proinflammatory cytokines [74]. In contrast, *Plasmodium falciparum*-free merozoites antagonize sCD40L-induced DC maturation by the activation of the ERK pathway [74].

Unlike p38 and JNK, ERK has been shown to play a role in preventing proper maturation of DCs [75]. DCs primed by helminth products often fail to show signs of classical maturation [65, 67, 76, 77]. The absence of DC maturation is in line with several studies in which stimulation of p38 MAPK was not observed in DCs exposed to helminth products such as SEA or LNFPIII from *Schistosoma mansoni* or the ES-62 antigen from *Filaria* [34, 63, 78]. Instead, these helminth-derived components preferentially induce the activation of ERK. Signaling through ERK in DCs results in the suppression of IL-12 and the induction of IL-10. As a result, ERK activation has been implicated in conditioning DC for Th2 priming [8]. Also, signaling through NF-κB appears to be important for priming of DC for Th2 polarization, since both SEA- and LNFPIII-pulsed NF-kB1-deficient DCs are incapable of inducing a Th2 response [79, 80].

ERK activation in DC primed by helminth products is also linked with inhibition of TLR ligand-induced maturation [63, 65, 67]. Kane et al. [63] have demonstrated that SEA dramatically reduces LPS-stimulated phosphorylation of p38, JNK, and ERK, as well as activation of NF-κB. In addition to generally inhibiting the phosphorylation of p38, SEA also delayed the kinetics of LPS-induced phosphorylation of this molecule. Thus, analyses of signaling pathways induced in DCs by SEA or by LNFPIII have indicated preferential activation of ERK1/2 in the absence of the activation of p38 [34, 69]. ERK signaling without p38 involvement was shown to lead to c-Fos stabilization and the suppression of IL-12 production [69]. Similar results were reported for human monocyte-derived DCs after exposure to LPS in combination with Th1-promoting bacterial extracts or Th2-promoting helminth-derived phospholipids from *Schistosoma mansoni* or *Ascaris lumbricoides*, all with TLR2's activating capacity. The analysis of signaling pathways activated upon exposure to LPS and the TLR2 activating compounds revealed that the ratio of activated MAPK p-ERK/p-p38 is lower in DCs stimulated with the bacterial products compared to DCs stimulated with the helminth products, which correlates with the Th1- and Th2-polarizing capacity of these compounds [81].

The induction of differential ERK activation in DCs is not exclusive of helminth parasites or its products. Different reports have linked ERK activation in DCs with impaired maturation after infection with *Leishmania amazonensis* or *Trypanosoma cruzi* [58, 82]. Infection of C3HeB/FeJ mice with *Leishmania major* results in a protective Th1 immune response [83] in contrast to that observed during *Leishmania amazonensis* infection which promotes an immature DC phenotype that results in a non-healing immune response [58]. In vitro infection of bone marrow-derived DCs (BMDCs) with *Leishmania amazonensis* amastigote results in rapid increase in ERK1/2 phosphorylation without changes in p38 and JNK compared with *Leishmania major* amastigote infection [58]. Moreover, during the infection of human monocyte-derived DC with *L. mexicana* promastigotes, the diminished phosphorylation of the MAP kinases JNK and p38 is associated to diminished DNA fragmentation. Hence, the authors hypothesized that the capacity of *Leishmania mexicana* promastigotes to diminish MAP kinase activation is one of the strategies employed to delay apoptosis induction in the infected DCs to favor the persistence of the parasite in the infected cells [84].

PI3K is a potent suppressor of IL-12 production by TLR-activated DCs [85]. Signaling pathways involved in the activation of PI3K have been implicated in parasite-induced negative regulation of DC maturation as well as IL-10 production. It is believed that pathogens use these signals to preferentially induce Th2-type response or to evade the development of Th1 protective immune response. In this regard, it is important to note, that among protozoan and helminth parasites, the activation of PIK3 and as well as ERK1/2 seems to play a main role in the interference of DC function. Thus, it has been demonstrated that *Giardia lamblia* as well as *Leishmania major* interferes with TLR-induced maturation through a PI3K-dependent pathway [57, 85]. Interestingly, ERK½- and PI3K-dependent pathways can be activated by engagement of CLRs [43], which links these pathways with Th2 induction by helminth parasites.

Together, these data indicate that different parasites or their products inhibit the ability of DCs to undergo proper maturation through activation of the ERK1/2 and PI3K.

Modulation of JAK-STAT mediated signaling

Cytokines mediate communication between cells of the immune system and are of crucial importance to induce an appropriately regulated immune response to invading pathogens. Cytokine receptor signaling has to be tightly controlled to balance antimicrobial and tissue-destructive effects, both of which are inherently associated with cytokine-mediated inflammation.

JAK/STAT families are two groups of proteins that constitute diverse signaling pathways involved in cytokine signaling [86]. JAK proteins sit at the apex of many cytokine receptor pathways, and their activation results in phosphorylation of the cytoplasmic domains of the receptor, leading to the recruitment and phosphorylation of STATs. In turn, the STATs induce transcription of a specific subset of genes, resulting in an appropriate cellular response that can include survival, proliferation, and/or cell differentiation. The STAT family is composed of seven proteins (STAT1-4, STAT5a, STAT5b, and STAT6), while the JAK family is composed of four proteins (JAK1, JAK2, JAK3, and TyK2). All of these proteins are constitutively present in the cytoplasm of DC without previous stimuli [86].

STAT1 is an important player in type I IFNs and IFN-γ signaling and therefore in the development and regulation of Th1-type immune response. The protozoan parasite *Toxoplasma gondii* can actively modulate cytokine-induced JAK/STAT signaling pathways in different cell types to facilitate survival within the host, including blocking IFN-γ-mediated-STAT1-dependent proinflammatory gene expression in APCs. *Toxoplasma gondii* active infection induces sustained STAT1 phosphorylation and nuclear translocation in BMDCs. However, in combination with IFN-γ, *Toxoplasma gondii* simultaneously blocks IFN-γ-induced STAT1 transcriptional activity avoiding the DC activation by IFN-γ [87]. In addition, during *Leishmania major* infection, STAT1 expression in DCs, but not T cells, is required for Th1-type immunity, because the absence of STAT1 resulted in impaired upregulation of MHC-II and costimulatory molecules and consequent reduction in Th1 cell priming [88]. Similarly, *L. amazoniensis* amastigotes have evolved unique strategies to actively downregulate early innate signaling events, including degradation of STAT2; decreased phosphorylation of STAT1, STAT2, and STAT3; and reduction in the expression of IRF-1 and IRF-8, resulting in impaired DC function and Th1 activation [89]. In addition, some products from parasite helminths can also modulate STAT1 signaling. As previously described, *Schistosoma mansoni* egg dsRNA induces DC STAT1 phosphorylation and activates a signaling pathway resulting in type I IFN- and IFN-stimulated gene expression via TLR3 engagement [39].

The transcription factor STAT4 participates in the IL-12 signaling pathway and this cytokine functions as the main physiological inducer of IFN-γ by activated T cells, driving Th1 differentiation [90]. In addition, IL-12 induces autocrine activation in DC being STAT4 central to this process. STAT4 is induced in DC in a maturation-dependent manner and in macrophages in an activation-dependent manner. Moreover, STAT4 levels directly correlate with IL-12-dependent IFN-γ production by DC during Ag presentation [91]. When IL-4 and IL-10 are present during DC maturation, they suppress STAT4 induction, diminishing IFN-γ production. In contrast, IL-4 has no effect on STAT4 levels in mature DC; it actually augments IFN-γ production by DC during Ag presentation, indicating that IL-4 acts on STAT4 in a spatiotemporal manner.

IL-4 and IL-13, the signature cytokines associated with the Th2 responses present during helminth parasitic infections [92], share a common receptor chain involved in signal transduction; thus, IL-4 and IL-13 are activators of STAT6 [93]. $STAT6^{-/-}$ mice display impaired Th2 differentiation and lose responsiveness to IL-4 and IL-13, but these animals are capable of maintaining normal responses to other cytokine signals. However, the importance of STAT6 and Th2 immune response are revealed in experimental models of infection with gastrointestinal parasites as *Trichinella spiralis* and *Nippostrongylus brasiliensis*, where the absence of STAT6 and consequently Th2 response is important for parasite expulsion [94]. Similar results were observed in filariasis and murine cysticercosis where STAT6 deficiency impairs the resistance to the infection [95, 96].

STAT6 signaling is constitutively activated in immature DCs and progressively declines as the cells differentiate into mature DCs [97]. Because IL-4R/IL-13R-associated STAT6 signaling is involved in DC maturation and IL-12 production [98, 99], the impaired resistance of $STAT6^{-/-}$ mice to

Toxoplasma gondii infection is linked to the lack of CD8+ T cell activation by STAT6$^{-/-}$ APCs [100]. In addition, splenic DC from *Toxoplasma gondii*-infected STAT6$^{-/-}$ mice show lower expressions of CD86 and production of IL-12 p40 than those from WT mice [100].

Induction of SOCS

JAK/STAT response requires tight regulation to prevent excessive inflammatory damage in the host, and the suppressor of cytokine signaling (SOCS) proteins are recognized as one of the most critical cellular mechanisms for controlling cytokine responses. SOCS are a family of eight intracellular cytokine-inducible proteins (SOCS1–SOCS7 and cytokine-inducible Src homology 2 (SH2)-containing protein (CIS)) [101]. SOCS are expressed basally in DCs and are rapidly induced by a variety of stimuli including cytokines and TLR ligands. Also, the SOCS proteins are transcriptionally regulated by the STATs and, by a variety of mechanisms, serve to inhibit JAK signaling in a classic negative feedback loop. All SOCS proteins negatively regulate JAK and STAT signaling through association of SH2 domain with phosphorylated tyrosine residues on JAK proteins and/or cytokine receptors. In addition, SOCS1, SOCS2, and SOCS3 have been shown to negatively regulate signaling through the degradation of signaling molecules via the E3 ubiquitin ligase activity of the SOCS box and ubiquitin–proteasome pathway. Only SOCS1 and SOCS3 contain a kinase inhibitory region (KIR) that is able to directly suppress JAK tyrosine kinase activity by acting as a pseudosubstrate, binding in or near the activation loop. [101].

SOCS1 and SOCS3 are induced as a consequence of TLR signaling and are capable of modifying the functional properties of APCs [102]. Thus, LPG from *Leishmania major* is able to induce SOCS1 and SOCS3 through TLR2 signaling [17]. Bartz et al. have reported that in human as well as murine precursor cells, TLR stimulation inhibits DC differentiation by induction of SOCS1 [103]. Accordingly, SOCS1-deficiency in APCs results in hyperactivation and consecutive hyper-Th1 responses and resistance to intracellular parasites as *Plasmodium berghei* ANKA [104]. Interestingly, SOCS1 and CIS are directly induced by viable *Toxoplasma gondii* tachyzoites inhibiting IFN-γ-signaling in murine macrophages [105]. Therefore, the induction of SOCS1 in host cells by the parasites might be part of its strategy to avoid the innate immune system.

SOCS3 is a critical negative regulator of cytokine responses that are dependent of the gp130 receptor (CD130) as IL-6 and IL-27. SOCS3 can also regulate, positively or negatively, IL-12 signaling by inhibiting STAT3 activation (which inhibits IL-12 signaling) or IL-12 induced-STAT4 activation, respectively [36]. SOCS3 expression is stimulated by cytokines or innate immune receptor agonists present in different pathogens [36]. During *Toxoplasma gondii* infection, SOCS3 expressed by DC indirectly promotes IL-12 production by limiting IL-6 induced STAT-3 signals [106].

Semnani et al. [62] have reported that live *Brugia malayi* microfilaria interferes with the function of monocyte-derived human DCs at different levels, from downregulating TLR4, TLR3, and MyD88 mRNA expression to the induction of SOCS1 and SOCS3 mRNA transcripts without altering the expression of costimulatory molecules. Similarly, ***Fasciola hepatica*** products, which inhibit TLR-induced DC maturation and function, upregulates the expression of SOCS3 but not SOCS1 on DCs [107].

In addition to regulating cytokine signaling, SOCS3 expression by DC plays a critical role in regulating indoleamine 2,3-dioxygenase (IDO) expression [108]. After immunogenic DC stimulation, SOCS3 has the ability to bind IDO and is responsible for its ubiquitin-mediated proteasomal degradation [108]. IDO catalyzes the initial rate-limiting step of tryptophan catabolism leading to the production of immunoregulatory catabolites collectively known as kynurenines. We and others have demonstrated IDO upregulation after infections with protozoa or helminth parasites [109–113]. IDO expressed by APCs has a dual role during the infections: on the one hand, IDO-competent DCs have a role in generating Treg cells that drive peripheral tolerance [114] and, on the other hand, IDO production of kynurenines or tryptophan degradation inhibits the growth of intracellular parasites as *Trypanosoma cruzi* or *Toxoplasma gondii* [111, 115, 116]. Therefore, although there have been no reports about parasite-induced regulation of SOCS3 and IDO in DCs, it is possible to speculate that, depending on the type of parasite infection, upregulation of SOCS3 could be a parasite strategy for immune evasion or a host tactic to antagonize IDO-dependent tolerogenesis and promote an effective T cell response able to eradicate the infection.

SOCS2 has E3 ubiquitin ligase activity and exclusively has the ability to target SOCS1 and SOCS3 for degradation. Thus, SOCS2 regulates the protein levels of SOCS1 and SOCS3, potentiating the signaling regulated by these proteins [117, 118]. SOCS2 is induced as a consequence of TLR stimulation in DCs. However, compared to SOCS1 and SOCS3, SOCS2 induction is delayed and Posselt et al. propose a model in which the delayed expression of SOCS2 provides a mechanism of late-phase counter-regulation and limitation of inflammation-driving DC activity [119]. A good example of this is the *Toxoplasma gondii* induced upregulation of SOCS2 associated to “DC paralysis” following the peak of IL-12 production [59]. The SOCS2 expression, achieved by the parasite-induced production of lipoxin A4 (LXA4), is dependent on aryl hydrocarbon receptor (AhR) activation [120], an intracellular receptor activated by ligands involved in the modulation of the inflammatory response [121]. Lipoxins, as well as the IDO-induced tryptophan metabolite L-kynurenine,

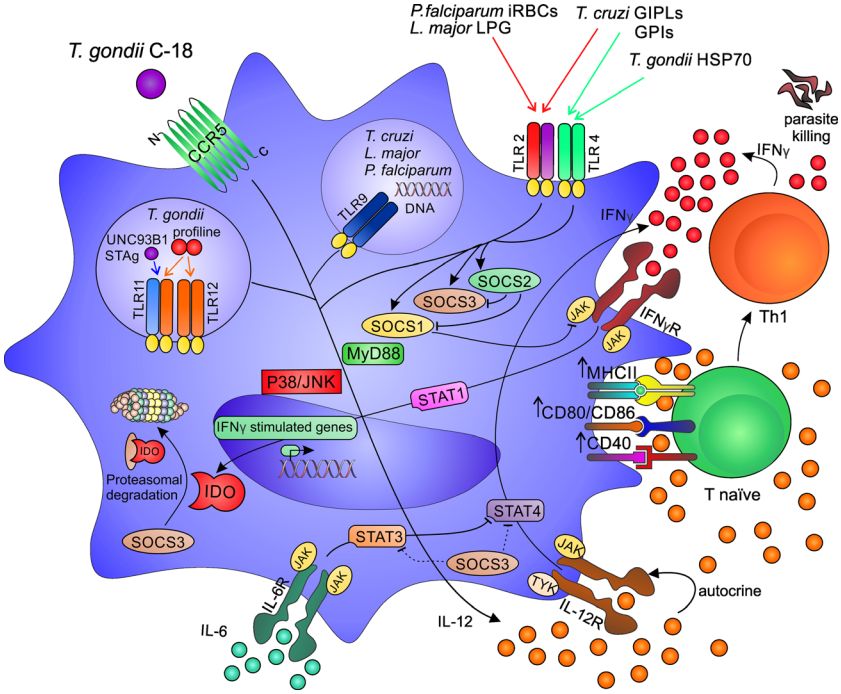

Fig. 1 Molecular mechanisms through which DCs are activated and regulated during protozoan parasite infections. Protozoan-derived molecules condition DC for Th1 polarization through interactions with PRR, which in signaling-dependent fashion (involving the activation of MAPKs p-38 and JNK) induce the expression of Th1-promoting molecules. Protozoan-derived molecules may favor instruction of Th1 responses by DC, by inducing antigen presentation, costimulation, and expression of the Th1-promoting cytokine IL-12. IL-12 autocrine activation in DC induces IFN-γ production by these cells during Ag presentation being STAT4 central to this process. Autocrine and paracrine (Th1- and NK cell-derived) STAT1-dependent IFN-γ signaling induces DC activation and the expression of IFN-γ-stimulated genes like IDO. SOCS are induced by cytokines and TLR ligation and through different mechanisms control cytokine responses. SOCS3 can inhibit IL-12 induced-STAT4 activation or indirectly promote IL-12 production by limiting IL-6 induced STAT3 signals. In addition, SOCS3 can drive proteasomal degradation of IDO

induce SOCS2-dependent ubiquitinylation and proteasomal degradation of TRAF6, hindering the proinflammatory cytokine expression by DCs [122]. Importantly, during *T.cruzi* infection in mice, the absence of SOCS2 results in immunopathology in the heart [123], indicating an important function for this protein in the inflammation control during this infection.

Other DC signaling pathways involved in the induction of Th2 response by helminth parasites

The requirements for DC to promote Th1 differentiation have been well established, but the signals through which DCs drive Th2 response have not been fully elucidated. Induction of Th2 development by DC is thought to be induced by weak TCR signaling, by expression of certain costimulatory molecules, and by the lack of IL-12 as well as by IL-4 and alarmins [124].

Thus, low antigen presentation or low affinity for the complex peptide/MHC-II favors Th2 responses [124]. Accordingly, it has been reported that omega-1-exposed DCs exhibit decreased antigen-dependent conjugate formation with $CD4^+$ T cells, suggesting that omega-1 interferes with antigen presentation, thereby lowering the strength of the activation signal delivered [125]. Also, helminth parasites express cysteine proteases, termed cathepsins, which lead to immune deviation by suppressing Th1 immunity [126]. In addition, there is substantial evidence showing that nematode parasites utilize proteinase inhibitors to protect themselves from degradation by host proteinases and also to manipulate the host immune response [127]. Cysteine proteases inhibitor (CPI, cystatin) is one of the major immune modulators produced by nematode parasites that modulate cathepsin activities and antigen presentation. As example, CPI from the murine nematode parasite *Heligmosomoides polygyrus* is able to modulate differentiation and activation of BMDCs and also interferes with antigen and MHC-II molecule processing and TLR signaling pathway, resulting in functionally deficient DCs [128].

The range of candidate molecules that DCs must express to efficiently induce Th2 responses is increasing. The expression of Notch ligand family members, delta-4 and jagged-2, has been associated with the induction of Th1 and Th2 responses, respectively [81]. However, the facts that the Th2-polarizing capacity of SEA-primed DCs deficient for Jagged-2 is unaffected, and that delta-4 antagonizes Th2 polarization and is

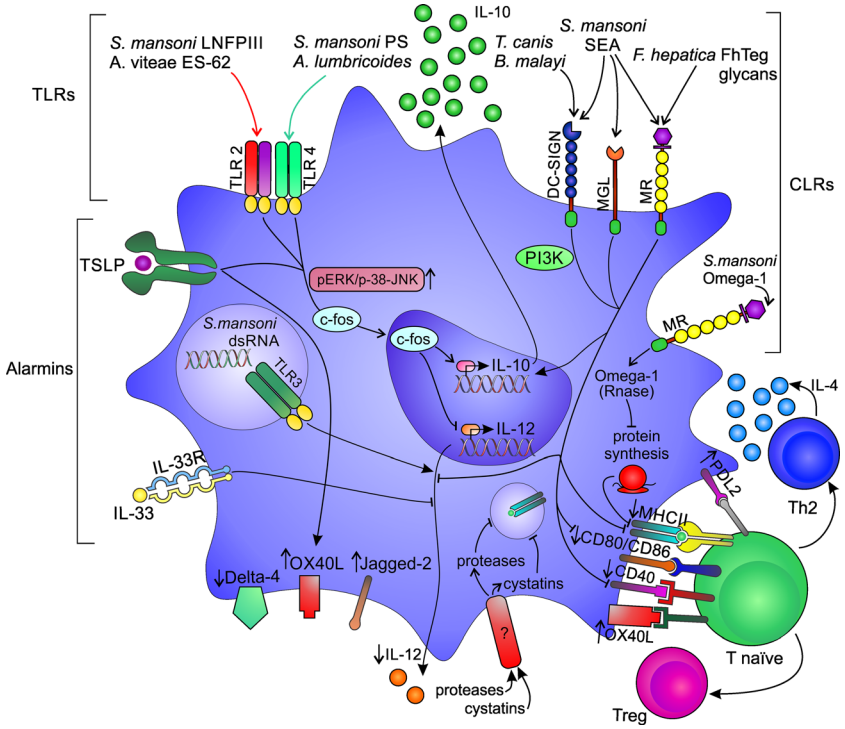

Fig. 2 Helminth and DC interactions. Helminth products condition DC for Th2 induction and Treg polarization through interactions with PRR such as TLRs, CLRs, or scavenger receptors, which in signaling-dependent fashion (involving MAPK ERK 1/2 phosphorylation, c-Fos upregulation and expression of SOCS) induce the expression of Th2-promoting molecules (as OX40L, jagged-2) while suppressing the expression of Th1-polarizing factors (as delta-4). Helminth products may also favor induction of Th2 responses by DC, by suppressing antigen presentation, costimulation, and/or expression of IL-12 through direct interference with these pathways. In addition, DC modulation for Th2 polarization includes endogenous host tissue factors called "alarmins," which are released in response to infection as TSLP and IL-33

downregulated by Th2-inducing lipids from *Schistosome* and *Ascaris* worms, suggest that selective inhibition of delta-4 may be a prerequisite for the priming of Th2 development [81]. Moreover, expression of OX40L has been shown to play an important role in Th2 polarization in vitro by SEA-primed DCs, although it does not appear to be a direct Th2-polarizing signal [129].

An interesting hallmark of DC activation by Th2-type antigens, such as SEA and ES antigens from *Fasciola hepatica* among others [63, 65, 77], is that the DCs fail to display the conventional set of stimulation events, such as cytokine production and surface activation marker expression. Despite this unconventional maturation, helminth products are still able to condition DCs to induce Th2 and Treg responses [65]. These last findings could be explained taking into account the complexity added to the knowledge of how the DCs interact with other cells, in the context of a helminth infection. Therefore, apart from helminth-derived components, several host-derived mediators called "alarmins" have been identified with the ability of exerting polarizing effects on DCs during helminth infection. Alarmins are naturally occurring endogenous mediators rapidly released in response to infection and/or tissue injury by several cell types. DCs are able to sense these "danger signals" through surface and intracellular receptors. Several alarmins have been described able to modulate DC function to drive Th2 polarization: thymic stromal lymphopoietin (TSLP), matrix metalloproteinase 2 (MMP-2), IL33, and eosinophil-derived neurotoxin (EDN) [130]. Particularly, during infection with intestinal nematode parasites, these worms or their products interact with intestinal epithelial cells promoting the secretion of different alarmins that include TSLP and IL-33 [6]. TSLP has been described to induce the upregulation of OX40L on DCs and modulate DC function driving Th2 responses [131]. However, while TSLP receptor knockout mice cannot develop a protective Th2 response to *Trichuris muris*, they do drive to a Th2-polarized response during infection with *Schistosoma mansoni*, *Heligmosomoides polygyrus*, or *Nippostrongylus brasiliensis*, suggesting a controversial role of TSLP in Th2 development [132]. IL-33 is another important alarmin implicated in the modulation of DCs to promote Th2 development. Stimulation of BMDCs with this cytokine promotes Th2 development. In addition, IL-33 treatment promotes Th2 cytokine production and expulsion of *Trichuris muris*, while mice with a deficiency in IL-33 receptor are unable to develop Th2-type response during *Schistosoma mansoni* infection [133]. Thus, the modulation of DCs to promote Th2 polarization is dependent not only on a direct effect of helminths or their products on these cells but also on the interaction with tissue-derived factors that also have an impact in DC activation.

Overview and clinical implications

Approximately one third of the world's population has been infected with parasites at some point in their lives; however, under natural conditions, severe host mortality directly attributable to parasitic infections is difficult to establish and has occasionally been reported [134]. Altogether, host mortality as observed during viral or bacterial epidemics is rarely caused by parasitic organisms alone.

It is assumed that during evolution, both host immune system and parasites have exerted reciprocal selective pressures on each other, which have led to rapid reciprocal adaptation to survival. The immune system is one of the most complex systems of an organism and shows many signs of coevolution with parasites. Thus, hosts arrange their immune system to prevent infections or keep the parasites in check, and often, a measured control of the infection by the host to avoid tissue damage is thought to be the cause of chronic infections. The pathological outcomes of infections arise when the degree of tissue damage or alteration of host physiology exceeds the capacity of tolerance mechanisms. Tolerance is considered to be the ability of the host to reduce or control the effect of an infection on host fitness. During parasite infections, the host can undergo two types of tissue damage: direct damage by the pathogen and immunopathology. Therefore, the host can achieve two types of tolerance mechanisms: one minimizing pathogen-induced damage, and the other one minimizing immunopathology [135]. As we described above, during almost all protozoan parasite infections, DCs are conditioned to mount the appropriate Th1 response able to eradicate the parasite (Fig. 1), and therefore, pathogen-induced damage, and this is obviously a fitness advantage. On the other hand, chronic infections as those caused by helminth parasites that have to migrate through the host tissues are frequently associated with severe, long-lasting pathology, and processes which minimize such complications could be more beneficial to the host than to the parasite attack. In this context, the modulation of maturation and function of DCs to induce Th2 or Treg responses (Fig. 2) is a crucial event for the generation of responses that do not cause damage to the parasite or the host.

Although, by definition, parasitosis is an undesirable condition for a host, because the parasite survives either by affecting the health of the host or at the expense of its nutritional deterioration, unexpectedly, it has been proposed that intentional infection of humans with helminths may become therapeutic in autoimmune diseases [136]. In several murine models of autoimmunity, the infection with helminth parasites or the treatment with helminth-derived products becomes protective [66, 137]. Currently, there are 28 clinical trials of helminth therapy in autoimmune diseases and related conditions, such as Crohn's disease, ulcerative colitis, multiple sclerosis, celiac disease, psoriasis, allergies, asthma, rheumatoid arthritis diseases, and autism [136]. However, concerns related to long-term effects, potential side effects, mixed pathogen infections, and purification of parasite immunomodulatory molecules remain to be addressed in order to achieve the use of helminths as anti-inflammatory agents for human diseases.

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